Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for misoprostol (gynaecological indication - termination of pregnancy), the scientific conclusions are as follows:

In view of available data on cardiovascular events (cardiac arrest, myocardial infarction and/or spasm of the coronary arteries and severe hypotension) from the literature, spontaneous reports including some cases with a close temporal relationship and in view of a plausible mechanism of action, the Lead Member State considers a causal relationship between on label use of misoprostol (gynaecological indication – termination of pregnancy) and cardiovascular events is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing misoprostol (gynaecological indication – termination of pregnancy) should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for misoprostol (gynaecological indication - termination of pregnancy) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing misoprostol (gynaecological indication - termination of pregnancy) is unchanged subject to the proposed changes to the product information.

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

Cardiovascular risk

Rare but serious cardiovascular accidents (**cardiac arrest**, myocardial infarction and/or spasm of the coronary arteries and severe hypotension) have been reported following ~~the intra-vaginal and intra-muscular administration of a high dose of prostaglandin analogue, including~~ **use of** misoprostol. For this reason, women with risk factors for cardiovascular disease (e.g. age over 35 years with chronic smoking, hyperlipidemia, diabetes) or established cardiovascular disease should be treated with caution.

[…]

- Section 4.8

The following information under the SOC vascular disorders with a frequency 'rare' should be amended:

Vascular disorders:

Rare but serious cardiovascular accidents (**cardiac arrest,** myocardial infarction and/or spasm of the coronary arteries and severe hypotension) have been reported ~~mainly~~ with the use of ~~non-authorised vaginal administration of~~ misoprostol.

Package Leaflet

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

The following side effects may occur:

Serious Side Effects

Serious side effects include:

- allergic reaction. Severe skin rashes such as itchy red spots, blisters or lesions.
- **cardiovascular accidents. Chest pain, difficulty breathing, confusion, or an irregular heartbeat. This may lead to cardiac arrest.**

Other serious side effects include:

- ~~cardiovascular accidents. Chest pain, difficulty breathing, confusion, or an irregular heartbeat.~~
- cases of serious or fatal toxic or septic shock. Fever with aching muscles, rapid heart rate, dizziness, diarrhoea, vomiting or feeling weak. [remove line break/line shift] These side effects may occur if you do not take this medicine orally or if you take it later than 49 days after the first day of your last menstrual period for a medical termination of pregnancy.

[…]

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 March 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	09 May 2024